

If any extension of time is required, please consider this paper a petition for the total extension of time required.

It is believed that no fee is due in connection with this paper. In the event that a fee is due, kindly refer to the general Deposit Account Authorization and Request for Automatic Extensions of Time previously filed with the application.

Claims 1-37 are pending in this application. Claims 14-37 were held to be withdrawn from consideration as being drawn to non-elected Claims.

Reexamination and reconsideration of the application, as amended, are respectfully requested.

**The Restriction Requirement -- Request for Clarification,  
and Conditional Authorization for Examiner's Amendment**

As stated in the Applicants' June 12, 2002 response to the restriction requirement, based on their similar subject matter and their identical classification, it is assumed that both Groups labeled as "II" in the March 1, 2002 restriction requirement were intended to form a single Group II. Applicants respectfully repeat a request that was made to the Office in the June 12, 2002 Response: Namely, the Office is respectfully requested to clarify that Group II includes each of Claims 14-23, 25, and 27-37. Should the Office's clarification suggest that the two Groups labeled "II" were in fact intended to denote separate Groups, then Applicants have reserved the right to traverse the election of species following that clarification.

If, on the other hand, the Office confirms that Group II indeed includes each of Claims 14-23, 25, and 27-37, then the Office is authorized to cancel by Examiner's amendment all Claims to the non-elected inventions, namely Claims 14-37. If Group II does not include each of the identified Claims, then this Examiner's amendment is not authorized, and in that case Applicants will consider an appropriate response in view of the clarification that is provided by the Office.

**The § 112, Second Paragraph Rejections**

Claims 1-13 were rejected under 35 U.S.C. § 112, second paragraph on several grounds. Specific grounds of rejection were made only for Claims 1, 2, 10, and 13, so it

is assumed that the remaining Claims were rejected based on their dependence from independent Claim 1.

### ***Claim 1***

Claim 1 was said to be indefinite in the phrase "if any." Some tissue samples will exhibit angiogenesis, while other tissue samples will exhibit no angiogenesis. In the latter case, no angiogenic vessels will be observed. An observation that there is no angiogenesis associated with a particular sample can provide useful and valuable information. Therefore it is appropriate and accurate for the Claim to refer to "angiogenic vessels, if any."

The Office also said that "it is uncertain as claimed what would be a 'time sufficient to allow angiogenic vessels' to grow, if there are . . . neither angiogenic vessels nor source of angiogenic vessels . . . ." It is respectfully submitted that not only is the limitation in question definite, but that it highlights the need for the phrase "if any" to which the Office also objected. The full limitation in question is incubating "for a time sufficient to allow angiogenic vessels, if any, to grow into the matrix . . . ." A person of ordinary skill in the art would readily understand this limitation to mean that the time is sufficient for angiogenic vessels to grow into the matrix -- assuming that there are angiogenic vessels -- and otherwise, the time is sufficient to demonstrate the fact that there are none, because angiogenic vessels would have grown into the matrix within the allotted "sufficient" time, had such vessels been present.

### ***Claim 2***

Claim 2 was said to be indefinite in its use of the word "substantially." The M.P.E.P. recognizes that the use of the term "substantially" is often definite, depending on context. See M.P.E.P. § 2173.05(b), subheading D. In the context of Claim 2, the term "substantially" is definite. The full expression appearing in the Claim is "wherein the medium contains substantially no exogenous angiogenesis-enhancing factors and substantially no exogenous angiogenesis-suppressing factors." In other words, it is not necessary to exclude every last molecule of any enhancing or suppressing factors. The

limitation is consistent with the complete absence of enhancing or suppressing factors. But a person of ordinary skill in the art would readily understand that the limitation is also consistent with the possible presence of small quantities of enhancing factors, or small quantities of suppressing factors, or both. However, if such a factor is present, then the observed angiogenesis of tissue samples in the medium should be substantially the same, on average, as would be observed in an otherwise identical medium that completely lacked the factor. If the observed average angiogenesis were substantially different from that in an otherwise identical medium that completely lacked the factor, then the medium would not be considered to be substantially free of the factor. A person of ordinary skill in the art would readily comprehend the meaning of these limitations. The Claim limitations in question are definite.

The Office further said: "This claim is also confusing in light of the other claims which are drawn to the use of serum (claim 3) and/or to the use of various factors (claims 4, 5 and 13)." The Office's comment is not understood. Claims 3, 4, 5, and 13 do not depend from Claim 2, so there is no reason why the limitations of Claim 3, 4, 5, or 13 should be consistent with the limitations of Claim 2. The Office is respectfully requested to withdraw this comment, or to clarify the comment so that a more responsive reply might be made.

### ***Claims 10 and 13***

Claims 10 and 13 have been clarified in a manner that is believed to overcome the § 112, second paragraph rejections in a self-evident manner that should not require extended discussion. The amendments to these Claims are intended as clarifications only, and are not intended to change the scope of the Claims in any manner.

### ***§ 112, Second Paragraph Summary***

It is respectfully submitted that all § 112, second paragraph rejections have been overcome or should be withdrawn.

### **The §§ 102 and 103 Rejections**

All examined Claims (i.e., Claims 1-13) were rejected under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 as being both anticipated by, and obvious over, one or more of four different references cited by the Office.

It is respectfully submitted that the claimed inventions are both novel and nonobvious over the cited references, whether those references are considered individually or in combination.

Claim 1 is the sole independent Claim within this Group of Claims. Without waiving the right to assert alternative arguments in the future, in the interest of brevity Applicants will only discuss Claim 1 for the time being. If independent Claim 1 is novel and nonobvious, then it logically follows that dependent Claims 2-13 must also be novel and nonobvious. Further in the interest of brevity, for the time being only a single reason will be argued why Claim 1 is distinguishable from the cited references, since that reason is particularly straightforward.

#### ***The "three-dimensional tissue sample" limitation***

Independent Claim 1 contains the following limitation that is neither taught nor suggested by any of the cited references:

"embedding a three-dimensional mammalian tissue sample in  
a matrix"

It is well-settled that a patentee is entitled to be his or her own lexicographer. The present specification contains a detailed definition of what is meant by a "three-dimensional" tissue or tissue fragment. The definition is followed by several specific examples of specimens that are considered to be "three-dimensional" within the scope of this definition, and several specific examples of specimens that are not considered to be "three-dimensional" within the scope of this definition. See the specification at page 28, line 22, through page 29, line 10:

### **Definition**

Any biological system will, in a literal sense, be three-dimensional. However, as used in the specification and Claims, a tissue or tissue fragment is considered to be "three-dimensional" if it has multiple layers of cells comprising blood vessels and other cells of the tissue, and if the architecture of the tissue or tissue fragment (including, for example, the blood vessels, supportive stromal elements such as fibroblasts, neural and endothelial cells) is substantially intact and has not been disrupted as compared to the comparable tissue *in vivo*. As examples, a tumor, tumor sample, other tissue, or other tissue sample is considered "three-dimensional" within the scope of this definition if its structure has not been disrupted. It may be sliced or reduced in thickness, so long as multiple layers of cells are retained, and so long as the relative structure and relation of blood vessels and other cells to one another is maintained.

As examples, the following would not be considered "three-dimensional" within the scope of the above definition: an isolated vein; an isolated artery; isolated cells from a disrupted tumor or other tissue; or an agglomerations of cells grown in culture -- even an agglomeration that has substantial thickness and is "three-dimensional" in the ordinary sense -- if the agglomeration lacks the architecture of the comparable tissue *in vivo* -- such as an agglomeration of tumor cells grown in culture without any vascularization.

Some of the advantages of the novel system are explained in the specification at page 15, lines 1-20, and page 21, lines 1 through 24:

No prior reports are known of angiogenesis assays for tumors or other tissue in which the intact three-dimensional structure of the tissue is maintained during the assay -- as opposed to, for example, reports of an assay conducted on an isolated artery or vein. . . .

We have discovered an *in vitro* tissue angiogenesis and vasculogenesis system that allows the outgrowth of microvessels from a three-dimensional tissue fragment implanted in a matrix. . . . This system, which may be used with human or other mammalian or animal tissues, may be used in assaying tumor angiogenic potential . . . . The angiogenic potential of a tissue can be determined by measuring the growth of microvessels into the matrix. The system is based on endogenous angiogenesis, vasculogenesis, neovascularization, or tissue perfusion, independent of tumor angiogenesis or other tissue angiogenesis. By contrast, tumor angiogenesis *per se* results from the formation of patterned networks of interconnected loops of extracellular matrix through which tumor perfusion may occur. The three-dimensional structure of the tumor or other tissue is maintained in the matrix, including its blood vessels, supportive stromal elements such as fibroblasts, and neural and endothelial cells. . . .

The invention allows a tumor or other tissue to induce an angiogenic response while maintaining an intact three-dimensional architecture.

The present invention offers several advantages. It allows the evaluation of a tumor or other tissue's angiogenic response while maintaining an intact three-dimensional architecture. Tumor (or other tissue) compartments may be evaluated simultaneously or separately. The novel system allows the evaluation of drugs that require activation *in vivo* and drugs that are active *ex vivo*. One advantage of this invention is that it may be used to provide a functional (as opposed to histological) angiogenic index. A functional angiogenic index may help to reveal tumors with a poor prognosis due to a high functional angiogenic index, even though they may have a low histological angiogenic index. A disparity between functional and histological angiogenic indices may occur if circulating anti-angiogenic

substances (such as angiostatin/endostatin) mask the angiogenic potential of a tumor. . . .

The invention may also be used to develop prognostic tests for a patient's resistance or susceptibility to the future development of malignancy or angiogenesis-related diseases.

With this background, a straightforward examination of the cited references readily reveals that none of them teaches or suggests the use of a "three-dimensional" tissue sample within the scope of the above definition.

***U.S. Patent 5,856,184***

The Office cited Col. 11, lines 15-40 of this patent. Col. 11, lines 16-20 of the '184 Patent describe the specimen used in the experiment: the thoracic aorta of a mouse was excised, fat was dissected away, and the aorta was sectioned into 1 mm segments. As stated in the examples following the detailed Definition found in the present specification, an isolated blood vessel (artery or vein) is not considered to be "three-dimensional" within the scope of the present definition. See the present specification at page 29, lines 5-6. Even less would a 1 mm segment of an isolated artery fit within this definition.

***Brown***

The Office cited the abstract and page 551, col. 1, lines 4-20 of Brown. The source of the vessel fragments discussed on page 551 is given on page 550, col. 1, under the heading "Preparation of blood vessel fragments." Superficial blood vessels were excised from the surface of human placentas, cut into 1- to 2-mm fragments, and freed of residual clots. As just discussed, an isolated blood vessel is not considered to be "three-dimensional" within the scope of the present definition, much less a 1 or 2 mm segment of an isolated blood vessel.

### **Montesano**

The Office cited the abstract, page 807 (it is assumed that "page 870" was intended) at the "Materials and Methods" section, and figures 1 and 2. Montesano's abstract does include the words "three-dimensional." However, there is no indication of any sort that Montesano had the present definition of "three-dimensional" in mind. Furthermore, Montesano's reference to a particular "three-dimensional" element was in fact a reference to a three-dimensional matrix, not a three-dimensional tissue sample. See the first two lines of Montesano's abstract. The samples used were described in the first paragraph of the "Materials and Methods" section on page 870. Tissues (from various sources) "were minced into small fragments in a drop" of saline. One may infer that the tissue fragments must have been considerably smaller than the size of a drop of saline. In the following paragraph, there is a further indication of the size of the "small fragments" where it is stated that the "tissue fragments were . . . allowed to sediment, and resuspended" in solution. The fragments must indeed have been small if it was necessary to allow them to sediment, and if they could be said to later be "resuspended." As stated in the examples following the detailed Definition found in the present specification, isolated cells from a disrupted tissue are not considered to be "three-dimensional" within the scope of the present definition, nor an agglomeration of such cells grown in culture -- even if the agglomeration has substantial thickness. See the present specification at page 29, lines 5-10.

### **Lugassy**

The Office did not cite any particular portion of Lugassy. To date, Applicants have not obtained a translation of this reference. For the time being, therefore, these remarks are based on the "Abridged English Version" on pp. 37-38. This reference does mention a "three-dimensional" element, but again, there is no indication that Lugassy had the present definition of "three-dimensional" in mind. To the contrary, the manner in which Lugassy's tumor model was prepared shows clearly that it was not a "three-dimensional" tissue sample within the scope of the present definition. Lugassy teaches away from the present invention. Rather than maintain an intact, "three-dimensional" tissue sample, Lugassy teaches the use of a "rebuilt" tumor model, in which cells from a lymphoma cell line were

mixed with angioma fibroblasts obtained by culturing explants from a human vascular angioma. The mixed cells were suspended in a collagen gel, which then grew into the "rebuilt" cancer. Cells from the "rebuilt" cancer became confluent in 4-8 weeks. This last statement implies that the cells were not confluent at an earlier time, i.e., that they were separated from one another. As just discussed, isolated cells are not considered to be "three-dimensional" within the scope of the present definition, nor is an agglomeration of such cells grown in culture – even if the agglomeration grows to substantial thickness. See the present specification at page 29, lines 5-10.

### ***§102 and 103 Summary***

It is respectfully submitted that all prior art rejections should be withdrawn.

### **The Information Disclosure Citation**

The August 9, 2002 Office Action enclosed a copy of the May 25, 2001 Information Disclosure Citation (PTO-1449) in which three of the four citations were stricken. The Office gave no explanation of any sort for striking these citations. It is respectfully submitted that these references were timely submitted, as evidenced by the attached copy of a return postcard from the Office acknowledging their receipt. (The copy of the postcard is attached below, following the Appendix of "clean" versions of the amendments.) In the event that these references might have been misplaced, additional copies of the three references are enclosed with a new Information Disclosure Statement. Because these references were properly and timely submitted, no fee should be due. The Office is respectfully requested to consider the references cited in the enclosed Information Disclosure Statement, and to return a copy of the enclosed PTO-1449 with the next communication concerning this application.

In the alternative, the Office is respectfully requested to explain its rationale for striking these citations, so that a more responsive reply might be made. In particular, the Office is respectfully requested to identify – with specificity – any subsection of 37 C.F.R. §§ 1.97 and 1.98 that the Office maintains has not been satisfied by Applicants with respect to these citations. The Office's attention is specifically directed to 37 C.F.R. §

1.97(h), which clearly contemplates the possibility that references cited in an Information Disclosure Statement might not be prior art to the application in which they are cited. A conclusion that a reference is not prior art is not a sufficient justification for striking it from an Information Disclosure Citation.

The Office is also advised that it is Applicants' intention to file an additional Information Disclosure Citation in the near future. Should the Office take this case up for action before the additional Information Disclosure Citation has been matched with the file, a telephone call to the undersigned would be appreciated.

### **Small Entity Status**

Applicants have not claimed small entity status in this application. A filing receipt that was mailed by the Office on August 10, 2001 made no reference to small entity status. For reasons that are not clear, the Office mailed an "Updated Filing Receipt" on January 28, 2002. The updated filing receipt included a line stating " \*\* SMALL ENTITY \*\* ".

For the record, Applicants repeat that no claim to small entity status has been made in this application. If the Office has previously calculated or refunded any fees as if the Applicants had claimed small entity status, then the Office is respectfully requested to make appropriate corrections, with particular reference to the duplicate original Deposit Account Authorizations that were submitted with the application as filed.

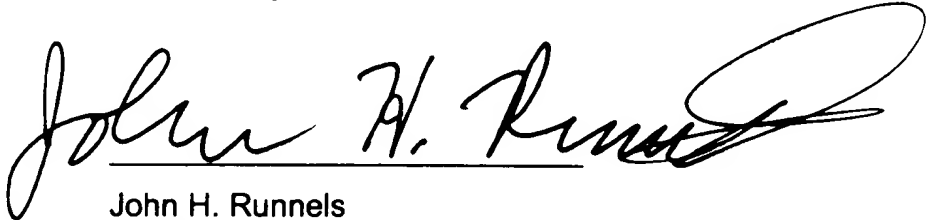
### **Conclusion**

The Office is respectfully requested to clarify that Group II of the Restriction Requirement includes each of Claims 14-23, 25, and 27-37. If the Office provides this confirmation, then the Office is authorized to cancel non-elected Claims 14-37 by Examiner's Amendment.

The Office is respectfully requested to consider the three references cited in the enclosed Information Disclosure Statement, and to return a copy of the enclosed PTO-1449 with the next communication concerning this application.

Allowance of all pending Claims at an early date is respectfully requested.

Respectfully submitted,

A handwritten signature in black ink, reading "John H. Runnels". The signature is fluid and cursive, with a large loop at the end of the last name.

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August 20, 2002

## Appendix -- "Clean" Version of Amendments

### Specification:

Paragraph at page 1, lines 13-14:

f The benefit of the May 30, 2000 filing date of provisional application 60/325,758 is claimed under 35 U.S.C. § 119(e).

### Claims:

Amended Claims 10 and 13:

f 1 10. (once amended) A method as recited in Claim 1, wherein the matrix  
2 comprises Matrigel™ matrix.

f 1 13. (once amended) A method as recited in Claim 1, additionally  
2 comprising the step of supplying a factor to the embedded tissue sample, and  
3 measuring the difference in angiogenesis for the tissue sample as compared to the  
4 angiogenesis of an otherwise identical and otherwise identically-treated control  
5 tissue sample that is not supplied with the factor; whereby the difference in  
6 observed angiogenesis is a measure of the angiogenic enhancement or angiogenic  
7 suppression characteristics of the supplied factor.